EXHIBIT G

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC. PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION **THIS DOCUMENT RELATES TO:** **WAVE 1 CASES ON ATTACHED EXHIBIT A**	**Master File No. 2:12-MD-02327** **MDL No. 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**

PLAINTIFFS' MEMORANDUM IN SUPPORT OF PLAINTIFFS' MOTION TO EXCLUDE THE OPINIONS AND TESTIMONY OF DEFENDANT ETHICON, INC. AND JOHNSON & JOHNSON'S EXPERT STEVEN MACLEAN, PH.D., P.E.

Plaintiffs in actions listed on attached Exhibit A, pursuant to Federal Rules of Evidence 702, 403, and 104, as well as the U.S. Supreme Court decision in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993), hereby respectfully moves this Court to exclude or limit the testing, opinions and testimony offered by Defendants Ethicon, Inc. and Johnson & Johnson's ("Ethicon") expert Steven Maclean, Ph.D., P.E.

INTRODUCTION

Ethicon designated Dr. Steven MacLean as an expert in this case. Like several other defense experts in this litigation, Dr. MacLean is employed by Exponent, Inc. Dr. MacLean – a Mechanical Engineer and Material Scientist – was hired by Exponent in 2011 to provide litigation services to industry clients like Ethicon and Johnson & Johnson.

> Q: You were hired by Exponent, in fact, according to this document, to help Exponent perform litigation services for industry clients, right?
>
> A: Correct.
>
> Q: Like Ethicon?
>
> A: Correct.

Q: Like Johnson & Johnson?

A: Correct.[1]

Unfortunately, Dr. MacLean attempts to offer opinions well outside his area of experience that are both unreliable and irrelevant. Specifically, the Defendants have designated Dr. MacLean to offer opinions in this case that: 1) Ethicon's Prolene-based stress urinary incontinence ("SUI") and pelvic organ prolapse ("POP") mesh devices are biocompatible; 2) Ethicon complied with the FDA regulations; 3) Ethicon's SUI and POP devices do not degrade; and 4) based on a set of experiments performed at Dr. MacLean's direction, intentionally oxidized Prolene does not stain when exposed to Hematoxylin and Eosin (H&E) histological dyes.[2,3] However, Dr. MacLean is not qualified to offer many of these opinions and the methodologies employed by him and others who assisted Dr. MacLean are unreliable. For the reasons set forth herein, the Court should exclude or, at the very least, limit Dr. MacLean's opinions pursuant to Federal Rules of Evidence 702, 403, and 104 and *Daubert*, 509 U.S. 579 (1993).

ARGUMENT AND AUTHORITIES

Plaintiffs incorporate by reference the standard of review for *Daubert* motions articulated by the Court in *Edwards v. Ethicon, Inc.*, No. 2:12-CV-09972, 2014 WL 3361923, at **1-3 (S.D.W. Va. July 8, 2014).

I. This Court Should Exclude or, Alternatively, Limit the Expert Testimony of Dr. Steven MacLean

Scientists from around the world, including Ethicon's own scientists, have demonstrated time and time again that polypropylene, including PROLENE, undergoes surface degradation

[1] Exhibit B - Deposition of Steven MacLean, Ph.D., P.E., Sept. 29, 2015, at 34:23-35:6.
[2] Exhibit C – Wave 1 Expert Report of Steven MacLean, Ph.D., P.E. (March 1, 2016) ("MacLean Report")
[3] Exhibit D – Wave 1 Supplemental Expert Report of Steven MacLean, Ph.D., P.E. (March 22, 2016) ("MacLean Supplemental Report")

after it is implanted in the body.[4,5,6,7,8,9,10,11,12,13,14,15] This opinion was confirmed by Ethicon's former scientist Dr. Thomas Barbolt who admitted under oath as Ethicon's 30(b)(6) witness that the PROLENE polypropylene material used to manufacture Ethicon's Prolene-based SUI and POP mesh kits undergoes *in vivo* surface degradation:

> **Q. And that's Ethicon's position as you – as the spokesperson for Ethicon, it's Ethicon's position that degradation, surface degradation, can occur, correct?**
>
> **A. Yes.**[16]

Despite the overwhelming evidence that PROLENE degrades *in vivo*, and the testimony of Ethicon's own 30(b)(6) witness, the Defendants have designated Steven MacLean, Ph.D., P.E. to rebut the conclusions of all of these scientists, including Ethicon's 30(b)(6) witness and the expert opinion testimony offered by Plaintiffs' experts who have all concluded that polypropylene, including PROLENE, is subject to *in vivo* degradation. In support of his

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[4] Exhibit E – Liebert, et al., "Subcutaneous Implants of Polypropylene Filaments." *Journal of Biomedical Materials Research*, (1976) 10(6):939–951

[5] Exhibit F – Jongebloed et al., "Mechanical and biochemical effects of man-made fibers and metals in the human eye, a SEM-study, *Documenta Ophthalmologica* (1986) 61, 303-3012

[6] Exhibit G – Mary, et al., "Comparison of the In Vivo Behavior of Polyvinylidene Fluoride and Polypropylene Sutures Used in Vascular Surgery" *ASAIO Journal*, (1998) 44(3):199–206

[7] Exhibit H – Clavé, et al., "Polypropylene as a Reinforcement in Pelvic Surgery Is Not Inert: Comparative Analysis of 100 Explants." *Int. Urogynecology J*., (2010) 21(3):261–270

[8] Exhibit I – Costello, et al., "Characterization of Heavyweight and Lightweight Poly." *J. Biomed. Mater. Res. B Appl. Biomater.*, (2007) 83B(1):44–49; Exhibit J - Costello et al., "Materials Characterization of Explanted Polypropylene Hernia Meshes," *J. Biomed. Mater. Res. B Appl. Biomater.*, (2007) 83B(1):44–49.

[9] Exhibit K – Wood, et al. "Materials Characterization and Histological Analysis of Explanted Polypropylene, PTFE, and PET Hernia Meshes from an Individual Patient." *J. Mater. Sci. Mater. Med.*, (2013) 24(4):1113–1122

[10] Exhibit L – Crack Depth In Explanted Prolene Sutures (June 15, 1982), ETH.MESH.12831405

[11] Exhibit M – Prolene (Polypropylene) Microcracks memo (March 23, 1983), ETH.MESH.15955438

[12] Exhibit N – Human Retrieval Specimens From Dr. Roger Gregory, Norfolk Surgical Group memo (March 29, 1983), ETH.MESH.15955440 (Ethicon's scientists used the same histological methods employed by Dr. Iakovlev to identify surface cracks observed on explanted Prolene sutures)

[13] Exhibit O – Examination of Prolene (Polypropylene) Sutures from Human Cardiovascular Explants memo (May 2, 1984), ETH.MESH.15955462 (Ethicon's scientists using the same histological methods as Dr. Iakovlev found that the explanted PROLENE suture had degraded in vivo. The histological stain penetrated the degraded PROLENE fiber. Blue dye particles were observed within the cracked layer confirming that cracked layer was PROLENE polypropyrlene and not a protein coating on the PROLENE strands)

[14] Exhibit P – IR Microscopy of Explanted PROLENE Received from Prof. R. Guidoin (Sept. 30, 1987), ETH.MESH.12831391-1404

[15] Exhibit Q – Seven Year Dog Study (Prolene 7-Year Dog Study) (Oct. 15, 1992), at ETH.MESH.09888220

[16] Exhibit R - Deposition Excerpt of Thomas Barbolt, Ph.D., January 8, 2014, at 409:2-8 (emphasis added).

opinions, Dr. MacLean submitted his Wave 1 Expert Report which was served on March 1, 2016.[17] After the expert disclosure deadline, Dr. MacLean also submitted a Wave 1 Supplemental Expert Report which contains, *inter alia*, his opinions concerning in vitro histology experiments performed under his direction of intentionally oxidized Prolene products manufactured by Ethicon.[18] As set forth below, Dr. MacLean is unqualified to offer many of the opinions expressed by him and the methodologies used by Dr. MacLean and his team are unreliable and irrelevant and must be excluded.

A. Dr. MacLean is Not Qualified to Offer Biocompatibility or Regulatory Opinions And His Opinions Concerning These Issues Are Unreliable

Throughout his expert reports, Dr. MacLean offers numerous opinions regarding the biocompatibility of Ethicon's Prolene-based products and its compliance with the FDA regulatory requirements when bringing these products to market which are all outside of Dr. MacLean's area of experience.[19] For example, in his expert report, Dr. MacLean opines that Prolene is biocompatible because "[t]he safety of PROLENE meshes has been demonstrated through a long history of clinical use in PROLENE sutures, as well as confirmatory cytotoxicity tests."[20] However, Dr. MacLean's deposition testimony demonstrates that he lacks the necessary expertise to offer opinions concerning the biocompatibility of Ethicon's Prolene-based mesh products:

- He is not a pre-clinical scientist.[21]
- He has never performed any biocompatibility assessments of Ethicon's mesh devices.[22]

[17] Exhibit C – MacLean Report.
[18] Exhibit D – MacLean Supplemental Report.
[19] *See e.g.*, Exhibit C – MacLean Report at 21-22 (Prolene biocompatibility and FDA regulatory compliance opinions).
[21] Exhibit B - MacLean Dep., 9/29/15, at 40:16-17.
[21] Exhibit B - MacLean Dep., 9/29/15, at 40:16-17.
[22] *Id.* at 40:23:41:1.

- He has never conducted any pre-clinical studies.[23]
- He has never looked at medical devices that were explanted from animals to determine whether or not they were biocompatible.[24]
- His only experience in analyzing the biocompatibility of the Prolene is in this case.[25]
- He has never performed any post-market testing of mesh implants prior to this case.[26]
- Prior to this litigation, he had never performed any failure analysis of a polypropylene suture.[27]
- Prior to this litigation, he has never studied the biocompatibility of polypropylene mesh for human tissue.[28]
- He has never published on the subject of biocompatibility of polypropylene mesh.[29]
- Prior to being retained as an expert in this case, he has never spoken or presented on the topic of polypropylene mesh.[30]
- He has never taught or lectured on the subject of polypropylene mesh.[31]
- He is not an expert on the biomechanical properties of the pelvic floor.[32]
- He is not a biologist or a molecular biologist.[33]

Moreover, his opinions in this regard are unreliable. In order to offer opinions concerning the biocompatibility of Prolene, it is necessary for an expert to consider the relevant clinical and pre-clinical studies. However, as Dr. MacLean testified, he did not adequately consider the relevant clinical and pre-clinical studies concerning the biocompatibility of Prolene mesh:

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[23] *Id.* at 41:7-9.
[24] *Id.* at 41:10-15.
[25] *Id.* at 41:22-42:1.
[26] *Id.* at 42:2-4.
[27] *Id.* at 46:17-47:4.
[28] *Id.* at 47:5-9.
[29] *Id.* at 47:10-13.
[30] *Id.* at 47:14-17.
[31] *Id.* at 47:18-20.
[32] *Id.* at 47:24-48:2.
[33] *Id.* at 48:3-6.

> Q Are you offering any opinions in this case regarding the cytotoxicity of the TVT material?
>
> A No, I'm not.[34]
> ****
> Q And you haven't looked at the clinical studies of the Prolene polypropylene mesh devices, correct?
>
> A I just don't remember. I don't remember if I've -- it was not a focus of my work. So if I saw them, I just don't remember them.[35]

As demonstrated above, Dr. MacLean's opinions are beyond his qualifications and are unreliable as he failed to conduct a proper analysis of the relevant data, including the clinical and pre-clinical studies.

Similarly, Dr. MacLean offers opinions concerning Ethicon's compliance with FDA regulatory requirement when it broght its Prolene-based SUI and POP mesh products to market yet Dr. MacLean is not a regulatory expert and has not demonstrated that he is qualified to offer these opinions.[36] By way of example, Dr. MacLean erroneously states that "…Ethicon obtained *approval* to market modified PROLENE, a mesh constructed of knitted filaments of extruded polypropylene, for repair of 'hernia and other fascial deficiencies'" and he cites to Ethicon, Inc.'s Modified PROLENE Polypropylene Mesh Nonabsorbable Synthetic Surgical Mesh 510(k) #962530 (emphasis added).[37] Ethicon goes on to state that "One of the earliest FDA-approved polypropylene-based products for female reconstructive surgery was Gynemesh® (Ethicon)."[38] Dr. MacLean either does not have the expertise to understand that Ethicon's mesh products were *cleared* rather than *approved* under the PMA process or he is intentionally misusing the term *approved* in an inappropriate effort to mislead the jury. As illustrated by Dr. MacLean's

[34] *Id*. at 158:23-159:1
[35] *Id*. at 160:2-7.
[36] Exhibit C – Steven MacLean CV attached as Appendix B to the MacLean Report.
[37] *Id*. at p. 25.
[38] *Id*.

intentional or negligent misuse of the term "approved" throughout his report discussing products cleared through the 510(k) regulatory pathway, the probative value of the FDA regulatory history of mesh devices is substantially outweighed by unfair prejudice, confusing the issues and misleading the jury and should be excluded in this case pursuant to Fed.R.Evid. 403 as has been done by this Court in other cases.[39]

When plaintiffs' in the Mullins' consolidated action challenged Dr. MacLean's qualifications to offer his biocompatibility and regulatory opinions, Ethicon – apparently recognizing Dr. MacLean's lack of qualifications in these areas – agreed that Dr. MacLean would "not offer opinions regarding biocompatibility or regulatory issues" in those cases.[40] Dr. MacLean is no more qualified to offer these opinions in the present cases than he was in *Mullins* and he should be precluded from doing so pursuant to FRE 702, 403, 104, 403 as well as the U.S. Supreme Court decision in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579 (1993).

B. Dr. MacLean's Molecular Weight Opinions Based on Ethicon's Seven Year Dog Study Should be Excluded as Unreliable

In 1985 Ethicon began a dog study to specifically research the potential for Prolene to degrade *in vivo* over time.[41] Ethicon's scientists implanted dogs with Prolene size 5/0 dyed, Ethilon size 5/0 dyed, Novafil size 5/0 dyed and PVDF size 5/0 undyed.[42] The study was supposed to last 10 years and data was reported at different intervals (2 years, 5 years, 6 years 10.5 months and 7 years). The study ended prematurely after 7 years and Ethicon's scientists, using various techniques, again concluded at the 7-year interval that the Prolene 5/0 suture that they tested demonstrated evidence of degradation:

IR Microscopy

[39] This issue will be the subject of a motion *in limine* that will be filed in this case at the appropriate time.
[40] Exhibit S – *Terry Mullins, et al., v. Ethicon, Inc. et al*, Case No. 2:12-CV-02952 (D.E. 227) (Nov. 9, 2015).
[41] Exhibit T – ETH.MESH.09888068
[42] *Id*. at ETH.MESH.09888069

> "IR spectra obtained for cracked PROLENE specimens (Figure A) showed possible evidence of slight oxidation (a broadened weak absorbance at about 1650 cm-1)."

Optical Microscopy and Scanning Electron Microscopy

> "Degradation in PROLENE is still increasing and PVDF, even though a few cracks were found, is still by far the most surface resistant in-house made suture in terms of cracking." [43]

Despite this evidence, Dr. MacLean relies heavily on the Gel Permeation Chromatrography (GPC) data obtained at the 7-year interval of the dog study for his opinion that Prolene does not degrade.[44] However, Ethicon's GPC data is unreliable. As stated above, in 1985 Ethicon implanted the dogs with Prolene 5/0 sutures; however, rather than run a control in 1985 using the same Prolene 5/0 suture that they implanted in the dogs, Ethicon instead compared the GPC data of the explanted Prolene 5/0 suture (implanted in 1985 and explanted in 1992) to the "current" Prolene 4/0 suture that was available in 1992.[45] Ethicon used an entirely different sized suture which was manufactured 7 years after the dog study was initiated as its control which is wholly unreliable.

As Dr. MacLean testified at his deposition, Ethicon should have determined the baseline of the test sample (i.e., Prolene 5/0) in 1985 when they started the dog study:

> Q. Yeah, I'm just trying to understand. So I'm not a scientist. So if there are variables or variability between one polypropylene to another polypropylene in the molecular weight, to -- if I'm going to do a study, I want to try to compare the same polymer as a control to the test article; is that right?
>
> A. If I want to look at -- are you suggesting that you're trying to investigate changes in molecular weight?
>
> Q. Yeah.
>
> A. And you need a baseline number?

[43] Exhibit U – ETH.MESH.09888187-188.
[44] Exhibit C – MacLean Report at 46-48.
[45] Exhibit U at ETH.MESH.09888187 and 09888218-22.

Q. Yeah.

A. And the baseline would -- you would want the baseline to be representative of the original material; is that what you're suggesting?

Q. Right, yeah.

A. I'd say in general that makes sense.

Q. Okay, because you want to -- you want to -- you want to reduce the variability?

A. Well, you need a reference point.[46]

However, in 1985, when Ethicon implanted the dogs with the Prolene 5/0 sutures, they never obtained a reference point in 1985 of Prolene 5/0 suture which Ethicon should have used as its control and its "baseline". Moreover, when asked whether he considered the molecular weight of a Prolene 5/0 suture, Dr. MacLean testified:

Q. Have you looked -- have you looked at the molecular weight of a 5-0 Prolene suture and compared it to the molecular weight of a 4-0 Prolene suture?

A. I don't recall.

Q. Have you asked for data from Ethicon to show you what the molecular weight is in a 5-0 compared to a 4-0?

A. No, I haven't asked for that.[47]

****

Q. What is the molecular weight of the control 5-0 that was ran in 1985?

A. I don't know if I've seen a document that says what the control of the 1985 5-0 is.[48]

Not only did Ethicon fail to use the appropriate control to eliminate the potential variability between the two different sutures but Dr. MacLean failed to even ask Ethicon's

[46] Exhibit B - MacLean Dep., 9/29/15, at 238:5-239:1
[47] *Id.* at 243:11-18.
[48] *Id.* at 247:14-17.

lawyers to provide him with data demonstrating what the molecular weight was of a 1985 Prolene 5/0 suture. Without demonstrating that the molecular weight of a 1985 Prolene 5/0 suture is the same as a 1992 Prolene 4/0 suture, Dr. MacLean is left to guess or assume the molecular weight is the same. *Rosen v. Ciba-Geigy Corp.*, 78 F.3d 316, 318-19 (7th Cir. 1996) (stating that "the courtroom is not the place for scientific guesswork, even of the inspired sort). Guesswork, even educated hunches, by an otherwise qualified expert is inadmissible. *Weis*gram v. Marley Co., 169 F.3d 514, 519-20 (8th Cir. 1999), aff'd 528 U.S. 440 (2000) (finding reversible error where trial court allowed expert witnesses to testify based on "rank speculation"). Thus, Dr. MacLean should be excluded from offering opinions concerning the unreliable GPC data from the 7 year dog study.

C. Dr. MacLean's Cross-Sectional Schematic and Calculated Theoretical Total Molecular Weight (Mn) of Excised 5-0 PROLENE sutures should be excluded as unreliable

On pages 77-78 of the MacLean Report, Dr. MacLean inappropriately extrapolates data from different studies to reach an unreliable opinion that Dr. Jordi's conclusions concerning the melt point of the Bellew explant are incorrect. Dr. Jordi conducted nano-thermal analysis on the surface of Ms. Bellew's explanted Prolift device and concluded that the drop in the melt point observed in Ms. Bellew's explanted Prolift device corresponded with a drop in the molecular weight of 4,500.[49] In an attempt to refute Dr. Jordi's findings, Dr. MacLean engages in math-magic first by using the melt point from the Bellew explant, then by assuming a crack depth of 4 microns, then by using Ethicon's dog study to demonstrate that the cracks are uniformly distributed over the surface of a 5-0 Prolene suture and finishes his magic trick by using the molecular weight data of the explanted 5-0 Prolene sutures from Ethicon's seven year dog study.

This analysis is flawed for several reasons. First, Dr. MacLean uses the molecular weight

[49] Exhibit C - MacLean Report at p. 77.

data from the dog study which is unreliable as discussed above. Second, he does not use the crack depth measurements from the dog study but instead "assumes" a crack depth of 4 microns from other studies while still using the molecular weight data from Ethicon's unreliable GPC data from its 1985 dog study. Extrapolation of data in this way is unreliable. If the crack depths in the dog study only measured 2 microns, Dr. MacLean's opinion would be erroneous:

> Q. So if you assume 4 microns, it gets you outside of the standard deviation for the molecular weight?
> A. At 4 microns, it does, correct.
> Q. At 2 microns, it gets you closer to the bulk analysis, which would wash out the molecular weight changes on the surface, they'd be masked by the bulk?
> A. It could. Yeah, at some smaller crust thickness, you would be within the statistical confines of the original data.[50]

Additionally, Dr. MacLean erroneously states that the dog study demonstrated that the cracks were uniformly distributed over the entire surface of 5-0 sutures which is used by Dr. MacLean in his calculation. However, the dog study did not conclude that the cracks were uniformly distributed throughout the entire surface of Prolene 5/0 suture. The best evidence regarding the distribution of the cracks observed in the dog study comes from the 6 year 10.5 month report which demonstrates that "[a]pproximately 50% of the PROLENE suture surface was cracked due to degradation."[51] Rather than rely on credible science to support his opinions, Dr. MacLean cherry-picked his data in an attempt to mislead or confuse the jury. Accordingly, Dr. MacLean should be excluded from offering this unreliable opinion.

D. Dr. MacLean Is Not Qualified To Offer Pathology Opinions and the Experiments He Relies On Are Unreliable

Dr. MacLean offers numerous pathology opinions throughout the MacLean Report and MacLean Supplemental Report which he is unqualified to offer. For example, Dr. MacLean

[50] Exhibit B - MacLean Dep., 9/29/15, at 278:23-279:8
[51] Exhibit T - ETH.MESH.09888100.

offers pathology opinions concerning: 1) artifacts in microtome processing; 2) opinions concerning Hematoxylin and Eosin (H&E) staining; and 3) opinions concerning artifacts related to histology and polarized light microscopy imaging.[52] However, Dr. MacLean is not a pathologist and is not qualified to offer these pathology opinions:

Q. You're not a pathologist?

A. Correct.

Q. And you're not an expert in pathology or histopathology analysis, correct?

A. Correct.[53]

Moreover, when asked if he routinely uses histological staining, Dr. MacLean admitted that he does not and that this was the first time he has ever asked for histological staining to be conducted:

Q. Do you routinely use histological staining?

A. I do not.

Q. When was the last time, other than this case, that you asked for or ordered some H&E staining to be done of explanted specimens?

A. This was the first time that I've actually done that, and that's exactly why we went to a third-party lab that specializes in it.[54]

Despite this, Dr. MacLean offers opinions concerning pathology and disputes the findings and opinions of Dr. Iakovlev and those of other experienced pathologists, including Ethicon's own, who have actually examined PROLENE devices explanted from human patients using the same histological methods employed by Dr. Iakovlev and concluded that explanted PROLENE degraded *in vivo* as demonstrated through histological staining and polarized light

[52] Exhibit C – MacLean Report at 40 (artifacts in microtome processing opinions); Exhibit D – MacLean Supplemental Report at 5 (pathology opinions concerning Hematoxylin and Eosin (H&E) staining); *Id*. at 28-31 (pathology opinions concerning histology and polarizing imaging artifacts).
[53] Exhibit B – MacLean Dep., 9/29/15, at 37:1-5
[54] *Id.*, at 395:4-11

microscopy.

For example, on May 2, 1984, Ethicon's scientists examined six samples of explanted PROLENE sutures by light microscopy.[55] The method used by Ethicon's pathologists was nearly identical to the histological methods employed by Dr. Iakovlev: "Pieces of tissue containing cross-sections of PROLENE suture were submitted for **histological preparation and staining with 1% aqueous Phloxine solution to enhance the visualization of the cracked layer."**[56] Ethicon's scientists reported that "histological sections of sample 6, a cracked surface layer measuring 3.0-4.5 microns was seen, accounting for approximately 8.5% of the total cross-sectional area."[57]

Just as Dr. Iakovlev describes in his report, Ethicon's own scientists observed that the cracked layer "was birefringent when examined under polarized light microscopy" and also as Dr. Iakovlev found "**Phloxin stain had completely penetrated the cracked layer**, Figure 5, or was confined to the periphery of the surface layer, Figure 6."[58] Ethicon's scientists observed that "**[p]articles of blue dye were evident within the cracked layer**, Figure 5."[59] Ethicon's scientists concluded:"[i]t was shown that a 5-0 PROLENE suture in residence within a human vascular graft for 7 years displayed surface cracking….The cracked layer appeared blue in gross specimens **and blue dye particles were evident in histological sections of the layer**. **This would indicate that the layer is dyed PROLENE polymer and not an isolated protein**

[55] See e.g., Exhibit O – Examination of Prolene (Polypropylene) Sutures from Human Cardiovascular Explants memo (May 2, 1984) , ETH.MESH.15955462 (Ethicon's scientists using the same histological methods as Dr. Iakovlev found that the explanted PROLENE suture had degraded in vivo. The histological stain penetrated the degraded PROLENE fiber. Blue dye particles were observed within the cracked layer confirming that cracked layer was PROLENE polypropylene and not a protein coating on the PROLENE strands)
[56] *Id*. at ETH.MESH.15955463
[57] *Id*. at ETH.MESH.15955464
[58] *Id*.
[59] *Id*.

coating on the stands."[60] Thus, Ethicon's own pathologist using the same histological methods that Dr. Iakovlev used reached the identical conclusions and opinions of Dr. Iakovlev – that Prolene degrades *in vivo*.

Dr. MacLean's criticisms to Dr. Iakovlev's opinions are based almost exclusively on his unreliable experiment where he used chemicals and ultra-violate (UV) radiation to intentionally oxidized samples of Prolene. Dr. MacLean sent his Prolene smaples to an outside pathology lab called Histion, LLC where the Prolene samples were embedded into paraffin or resin and then stained using Hemotoxylin and Eosin (H&E). According to Dr. MacLean, the intentionally oxidized Prolene samples did not stain. Dr. MacLean uses these results to refute Dr. Iakovlev's opinions that H&E will stain the outer layer of degraded Prolene. However, Dr. MacLean's opinions are unreliable or irrelevant because:

1) Dr. MacLean's experiment did not replicate the human condition where Ethicon's Prolene-based mesh products are implanted;

2) Dr. MacLean failed to adhere to the protocol used by Dr. Iakovlev; and

3) Dr. MacLean and/or the Histion manipulated the results through selection bias.

For these reasons and as set forth in greater detail below, Dr. MacLean should be precluded from offering any opinions or testimony derived from his unreliable and irrelevant experiment.

i. Dr. MacLean's experiments are unreliable because they did not replicate *the in vivo* human condition

Dr. MacLean attempted to intentionally degrade samples of Prolene by exposing them to certain chemicals for a period of approximately five weeks. He also attempted to oxidize samples by exposing them to ultra-violate light in a QUV weathering machine for several days at elevated temperatures to accelerate the degradation process. Upon completing these steps, Dr.

[60] *Id*. at ETH.MESH.15955464-5465 (emphasis added). See also *Id*. at ETH.MESH.15955468.

MacLean sent the samples to a pathology laboratory to be processed and stained with H&E stains. According to Dr. MacLean, none of the samples trapped the H&E stains.[61] However, exposing these Prolene samples to chemicals for only five weeks is not sufficiently long enough to replicate the *in vivo* degradation process that occurs within the human body sufficient to cause the outer layer of the samples to crack and trap the H&E staining. In a publication by Clave et al., degradation of polypropylene pelvic mesh was observed only in samples implanted for at least 3 months.[62] The use of UV radiation also does not replicate the degradation process that occurs in the human environment. As explained by Clave, the *in vivo* degradation process is complex and involves not only oxidation but other factors not replicated by ultra-violate radiation, including absorption of cholesterol and esterified fatty acids into the amorphous zones of polymer matrixes and free radical attack: "The chronic inflammatory reaction may infer free radical synthesis as peroxide and superoxide ions and hypochlorite acid. Once in contact with the PP implant, these radical species could infer an oxidation of C-H bonds. This oxidation could occur in the absence of oxygen, and the resulting free radicals could recombine and cross-link, altering the physical and mechanical properties of the polymer."[63]

When Dr. MacLean was deposed on this very issue he testified that neither of his experiments (chemical and UV degradation) replicated the *in vivo* condition of a woman's body:

> Q. And were you trying to mimic the *in vivo* environment where these meshes are placed in a woman's body?
>
> A. No, not at all.
>
> Q. Did any of your experiments mimic the *in vivo* environment of a woman's body?

[61] Exhibit D – MacLean Supplemental Report at 26-27.
[62] Exhibit H - Clave et al., *Polypropylene as reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants*, Int. Urogynecol J (2010) 21:261-270
[63] *Id*. at 267.

A. No.[64]

In *Sanchez v. Boston Sci. Corp.*, No. 2:12-CV-05762, 2014 WL 4851989, at *9 (S.D.W. Va. Sept. 29, 2014), *reconsideration denied*, No. 2:12-CV-05762, 2014 WL 5320559 (S.D.W. Va. Oct. 17, 2014), this Court excluded the opinions of one of the plaintiff's expert, Dr. Barker, after finding that Dr. Barker's experiment was unreliable because it did not replicate the *in vivo* environment inside the female pelvis.[65] Dr. MacLean's experiment and his opinions derived therefrom suffer from the same flaw and should similarly be excluded.

ii. Dr. MacLean's experiment is unreliable because he failed to adhere to the histology staining protocol used by Dr. Iakovlev

According to Dr. MacLean, the intentional oxidation experiment conducted under his direction was intended to act as a control of Dr. Iakovlev's study.[66] In this regard, Dr. MacLean testified that it was important that his experiment followed the same histological staining protocol that Dr. Iakovlev uses when he stains explanted mesh devices for his histopathology analysis;

Q. So it was important for your control experiment, since it's a control, to follow the protocol that was outlined by Dr. Iakovlev.

A. Correct.

This is why the protocol developed by Dr. MacLean required his Paraffin-embedded "control" samples to be "prepared and stained following the protocol submitted by Dr. Iakovlev."[67] Dr. Iakovlev's staining protocol is described in his peer-reviewed scientific article[68]

[64] Exhibit V – Deposition of Steven MacLean, Ph.D., P.E. 4/18/2016, at 120:6-14
[65] Exhibit W - *Sanchez v. Boston Sci. Corp.*, No. 2:12-CV-05762, 2014 WL 4851989, at *9 (S.D.W. Va. Sept. 29, 2014), *reconsideration denied*, No. 2:12-CV-05762, 2014 WL 5320559 (S.D.W. Va. Oct. 17, 2014) (This Court ruled that "because Dr. Barker's method did not account for the multi-directional forces inside of the female pelvis, his opinions about the effect of the mesh once implanted *in vivo* are unreliable and do not survive *Daubert* scrutiny). *See also*, Eghnayem v. Boston Sci. Corp., 57 F. Supp. 3d 658, 683 (S.D.W. Va. 2014)
[66] Exhibit V – MacLean Dep., 4/18/16, at 49:21-23.
[67] Exhibit X – Dr. MacLean's Histology Embedding and Staining Protocol for PROLENE Mesh and Sutures.
[68] Exhibit Y – Iakovlev, et al. *Degradation of polypropylene in vivo: A microscopic analysis of meshes explanted*

and required that his mesh explants be stained on charged coated slides with numerous histology stains including: 1) haematoxylin and eosin (H&E), and 2) Mason trichrome. His protocol further required the staining to be done manually on horizontal trays.[69]

Dr. Iakovlev has demonstrated that the degraded layer of polypropylene explants will trap H&E and trichrome stains.[70] The polypropylene explants stained with trichrome stains the deeper parts of the degraded "bark" red and the "degraded" bark closes to the surface green. As explained by Dr. Iakovlev, when polypropylene undergoes *in vivo* degradation, the surface layer develops nano-cavities as shown by Transmission Electron Microscopy[71] which causes the H&E to become trapped in the degraded outer layer and which also results in the different coloring seen at the different layers of the degraded bark layer when stained using trichrome.[72] Dr. MacLean's experiment failed to adhere to Dr. Iakovlev's protocol by only using H&E staining and not adding trichrome when these samples stained.

Moreover, Dr. MacLean testified that his intentionally oxidized samples were oriented on vertical trays when they were stained rather than horizontal trays that Dr. Iakovlev's protocol required.[73] The whole purpose of Dr. MacLean's study was to determine whether oxidized Prolene stains when following the staining protocol used by Dr. Iakovlev. This is especially important in this case where Dr. MacLean was attempting to conduct his study as a "control" of the work performed by Dr. Iakovlev. As this Court has previously recognized in excluding other mesh experts: "[v]igorous adherence to protocols and controls are the hallmarks of "good science." *Sanchez v. Boston Sci. Corp.*, No. 2:12-CV-05762, 2014 WL 4851989, at *28 (S.D.W.

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from patients, Society for Biomaterials (July 30, 2015), at pp. 2-3.
[69] *Id*.
[70] *Id*. at 5.
[71] Exhibit X at 8.
[72] Importantly, Dr. Iakovlev stained explanted specimens with Von Kassa (to rule out biological material - calcium) and immunohistochemical stain (to further rule out biological material – immunoglobulin), the degraded surface layer (degraded "bark") failed to stain.
[73] Exhibit V - MacLean Dep., 4/18/16, at 78:2-6; 80:24-81:5.

Va. Sept. 29, 2014), *reconsideration denied*, No. 2:12-CV-05762, 2014 WL 5320559 (S.D.W. Va. Oct. 17, 2014) (citing *Black v. Rhone–Poulenc, Inc.*, 19 F.Supp.2d 592, 603 (S.D.W.Va.1998)). Because Dr. MacLean failed to vigorously adhere to Dr. Iakovlev's staining protocol, his opinions concerning his experiments are unreliable and should be excluded.

iii. Dr. MacLean experiment and related opinions are unreliable

Critical to Dr. MacLean opinion is his claims that the intentionally oxidized samples from his experiment did not stain. Dr. MacLean argues that based on this finding, Dr. Iakovlev's opinions are unreliable. As an initial matter, Histion, LLC - the laboratory used by Dr. MacLean for embedding and staining the Prolene samples from his experiment - is not a clinical pathology laboratory. In other words, Histion does not analyze human pathology material for the purpose of diagnosing human conditions.[74] Just yesterday, Ethicon produced the laboratory notebook that was maintained by Histion documenting the work it performed histologically processing and staining the Prolene samples from Dr. MacLean's experiment.[75] At best, Histion's lab notebook demonstrates significant flaws in Histion's work embedding and staining Dr. MacLean's intentionally oxidized Prolene samples. At worst, the lab notebook demonstrates intentional selection bias carried out for the sole and improper purpose of manipulating the results of the experiment.

Histion's lab notebooks shows that it received 46 Prolene samples from Dr. MacLean: 22 of those were embedded in Paraffin and 24 were embedded in Resin.[76] These samples were embedded in Paraffin and Resin so they could be microtomed (sliced), adhered to pathology slides and histological stained with H&E. An important step in this process is removing the paraffin and resin for appropriate staining.

[74] Exhibit V – MacLean Dep., 4/18/16, at 75:16-23; 76:8-77:4.
[75] Exhibit Z – Histion Laboratory Notebook for project H16-008.
[76] *Id*. at p. 1.

Histion's lab notebook demonstrates that on March 12, 2016, Histion attempted to stain 20 slides that were initially embedded in Paraffin.[77] According to handwritten notes contained within Histion's lab notebook, all 20 slides failed to pass quality control "[d]ue to overstaining with Eosin." Dr. MacLean entire opinions concerning his experiment rests on his conclusion that oxidized polypropylene does not stain. If this were true, then it should have been equally as impossible to "overstain" these intentionally oxidized Prolene samples. It appears that Histion and/or Dr. MacLean did not like these results so Histion stained additional samples apparently from the same paraffin block.[78] However, this time Histion added additional steps by rinsing these samples with water after staining them with eosin which then required them to treat these samples with an additional 70% alcohol.[79] This was a deviation from Dr. MacLean's protocol[80] and likely washed away the stain. Ultimately, these are the slides that Dr. MacLean relied upon for his opinions.

Histion's lab notebooks similarly demonstrate that on March 14, 2015, Histion attempted to stain 23 slides that were embedded in resin (Technovit). However, these slides did not pass quality control either, apparently because this time the "Technovit plastic surrounding specimens stained too dark with eosin."[81] On the following day, Histion restained slides from the same resin block but changed its protocol yet again by skipping the initial treatment of 100% alcohol that it did the day prior.[82] This not only demonstrates that the staining procedure carried out by Histion was flawed but it also explains why the Prolene samples could not be stained after embedding them in resin – they were surrounded by Technovit plastic which made staining

[77] *Id*. at 12.
[78] *Id*. at 17.
[79] *Id*. (see step 15 and 16).
[80] Exhibit X – Dr. MacLean's Histology Embedding and Staining Protocol.
[81] Exhibit Z – Histion Laboratory Notebook at 8.
[82] *Id* at 8-9

impossible.

As demonstrated, the initial staining that was initially performed 43 or more paraffin and resin embedded slides allegedly "failed" quality control. Histion restained additional samples but only after deviating from its original protocol. If Dr. MacLean's opinion were correct - that intentionally oxidized Prolene will not stain then – following Dr. MacLean's logic – it would be impossible to overstain these oxidized Prolene samples. Histion decided to restain these Prolene samples because either it or Dr. MacLean did not like the results – which demonstrated that intentionally oxidized Prolene does stain (just too much), substantiating Dr. Iakovlev's opinions. Histion then deviated from its protocol which likely caused Dr. MacLean's intentionally oxidized Prolene slides to appear unstained or the protocol used by Histion did not remove the paraffin or resin which encased the Prolene samples which prevented stain from reaching its target – the Prolene fibers. In any case, Dr. MacLean's opinions are unreliable and should be excluded.

CONCLUSION

For the foregoing reasons, Plaintiffs respectfully request that this Court grant their Motion to Exclude or, Alternatively, Limit the Opinions and Testimony of Dr. Maclean, Ph.D., P.E.

Dated: May 14, 2016.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on May 14, 2016, I electronically filed the foregoing document with the Clerk of the court using CM/ECF system which will send notification of such filing to the CM/ECF participants registered to receive service in this MDL.

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